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ORIGINAL RESEARCH

Clinical features of patients with HER2-positive breast cancer and development of a nomogram for predicting survival

Y. Fan[1,2,3*], Y. Wang[4], L. He[1,2,3], S. Imani[1,2,3] & Q. Wen[1,2,3]

[1]Department of Oncology, The Affiliated Hospital of Southwest Medical University, Luzhou; [2]Nuclear Medicine and Molecular Imaging Key Laboratory of Sichuan Province, Luzhou; [3]Academician (Expert) Workstation of Sichuan Province, Luzhou; [4]Health Management Department, The Affiliated Hospital of Southwest Medical University, Luzhou, P. R. China

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Background: Different estrogen receptor (ER) and progesterone receptor (PR) expression patterns have important biological and therapeutic implications in patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer. However, little is known about hormone receptor (HR)-positive and triple-positive subtypes, making therapy selection and survival prognosis difficult. This study investigated the clinical characteristics and nomogram-predicted survival of patients with HER2-positive breast cancer.

Materials and methods: Data on patients with HER2-positive breast cancer were retrieved from the Surveillance, Epidemiology, and End Results database. Comparisons were carried out between single HR-positive and double HR-positive/double HR-negative subtypes. A nomogram-based model of predicted outcomes was developed.

Results: This cohort study included 34 819 patients with breast cancer (34 606 women and 213 men). Single HR-positive and double HR-positive/double HR-negative subtypes showed distinct clinicopathological characteristics. Multivariable Cox regression analysis showed that patients with ER-positive/PR-negative/HER2-positive [hazard ratio (HR) = 1.24; 95% confidence interval (CI): 1.14-1.39], ER-negative/PR-positive/HER2-positive (HR = 1.56; 95% CI: 1.23-1.97), and ER-negative/PR-negative/HER2-positive (HR = 1.56; 95% CI: 1.43-1.70) subtypes had worse breast cancer-specific survival than patients with the triple-positive subtype. Thirteen clinical parameters were included as prognostic factors in the nomogram: age, sex, race, grade, histology type, bone, brain, liver, and lung metastasis, TNM (tumor—node—metastasis) staging, and molecular subtype. The C-index was 0.853 (95% CI: 0.845-0.861). Calibration plots indicated that the nomogram-predicted survival was consistent with the recorded 3-year and 5-year prognoses.

Conclusions: Significant differences in survival rates were observed between single HR-positive and double HR-positive/double HR-negative subtypes. A nomogram accurately predicted survival. Different treatment strategies may be required for HER2-positive patients with single HR-positive and double HR-positive tumors to ensure optimal treatment and benefits.

Key words: HER2-positive breast cancer, clinical features, triple-positive breast cancer, nomogram, breast cancer-specific survival

INTRODUCTION

Breast cancer is a heterogeneous disease that exhibits substantial diversity in terms of genotypic and phenotypic profiles.[1,2] Human epidermal growth factor receptor 2 (HER2) overexpression is reported in ∼15%-20% of primary breast carcinomas and is associated with poor prognosis, and nearly half of HER2-positive breast cancers also express hormone receptors (HRs).[3,4] HR-positive/HER2-positive breast cancers are associated with better survival rates than HR-negative/HER2-positive breast cancers.[5] In addition, the majority of estrogen receptor (ER)-positive breast cancers also express progesterone receptor (PR). Although the presence of normal PR levels suggests an intact ER signaling pathway, different expression patterns of ER and PR (ER positive/PR negative and ER negative/PR positive) are often observed in breast cancer cells, and these subtypes are biologically and clinically different from double HR-positive/double HR-negative subtypes.[6-8] Chemotherapy plus anti-HER2 agents remains the mainstay of treatment for patients with HER2-positive breast cancer, despite the different therapeutic responses of different molecular

*Correspondence to: Dr Yu Fan, Department of Oncology, The Affiliated Hospital of Southwest Medical University, Nuclear Medicine and Molecular Imaging Key Laboratory of Sichuan Province, Academician (Expert) Workstation of Sichuan Province, #25 Taiping Street, Jiangyang District, Luzhou City, Sichuan Province, P. R. China. Tel: +86-830-3165613; Fax: +86-830-3165613
E-mail: yufan@swmu.edu.cn (Y. Fan).

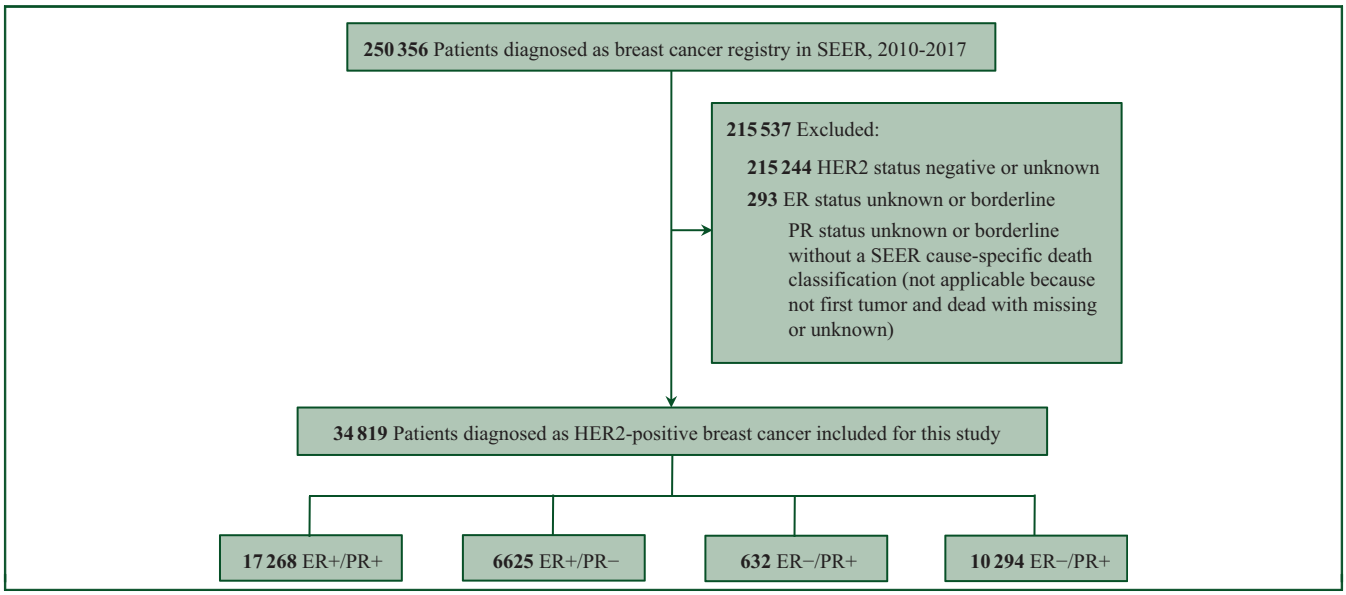

Figure 1. Flowchart of patient selection.
ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor; SEER, surveillance, epidemiology, and end results.

subtypes of HER2-positive breast cancer. The mechanisms underlying the effect of HR expression on reducing chemosensitivity in HER2-positive breast cancer remain unknown.[9,10]

The demographic characteristics, clinicopathological significance, and survival outcomes of patients with HER2-positive breast cancer, especially those with single HR-positive tumors, are not fully defined. In this retrospective cohort study, we investigated the clinical characteristics and survival prognoses of patients with HER2-positive breast cancer based on the population from the Surveillance, Epidemiology, and End Results (SEER) database. To guide therapeutic decisions on different subtypes of HER2-positive breast cancer, we carried out a systematic analysis and established a nomogram-based model of predictive outcomes. The study identified significant differences in survival prognosis among patients with different subtypes of HER2-positive breast cancer and established a nomogram that accurately predicts breast cancer-specific survival (BCSS) in patients with HER2-positive breast cancer based on independent prognostic factors.

MATERIALS AND METHODS

Data source

We obtained breast cancer individuals' data from the SEER database that were released in November 2019 using SEER*Stat 8.3.8 (National Institutes of Health, Bethesda, MD). These data include demographic, clinicopathological, and survival information. Our work followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines. The cohort included 250 356 patients with breast cancer originally identified from the SEER database. Because the SEER database started collecting the HER2 status in 2010, the year of diagnosis with breast cancer was considered as 2010. Patients diagnosed with HER2 status negative or unknown ($n = 215\,244$) were excluded. Patients with ER status unknown or borderline, PR status unknown or borderline, and without a SEER cause-specific death classification were also excluded ($n = 293$) (Figure 1).

A total of 34 819 patients with HER2-positive breast cancer were included in this cohort study. The demographic features were extracted: age at diagnosis, sex, and race. The clinical characteristics included bone metastasis status, lung metastasis status, liver metastasis status, brain metastasis status, adjusted American Joint Committee on Cancer (AJCC) seventh edition stage, tumor grade, histology type, ER status, PR status, T-staging, N-staging, M-staging, survival months, and cause of death. The molecular subtypes of HER2-positive breast cancer were characterized as ER positive/PR positive/HER2 positive (triple positive), ER positive/PR negative/HER2 positive, ER negative/PR positive/HER2 positive, and ER negative/PR negative/HER2 positive. Patients were stratified into the age subgroups of younger than 30, 30-39, 40-49, 50-59, 60-69, 70-79, and 80 years or older. Race was categorized as White, Black, Asian or Pacific Islander, American Indian/Alaska Native, and unknown. Grade was divided as well differentiated (grade I), moderately differentiated (grade II), poorly differentiated (grade III), undifferentiated (grade IV), or unknown. Patients were subgrouped according to T-staging (T0/is, Tmi/1, T2, T3, T4, and unknown), N-staging (N0/is, Nmi/1, N2, N3, and unknown), and M-staging (M0, M1, and unknown). Histology type was characterized as invasive ductal carcinoma (IDC) [International Classification of Diseases for Oncology, Third Edition (ICD-O-3) code 8500/3], invasive lobular carcinoma (ILC) (ICD-O-3 code 8520/3), mixed IDC and ILC (ICD-O-3 code 8522/3), or other types, according to ICD-O-3 histopathology codes.

The informed consent from patients was waived because of the public nature of the SEER database in accordance

Table 1. Characteristics of patients with HER2-positive breast cancer based on the SEER database, 2010-2017[a] [*n*/total *n* (%)]

Characteristics	All patients	Triple positive	ER+/PR−/HER2+	ER−/PR+/HER2+	ER−/PR−/HER2+
n	34 819	17 268 (49.6)	6625 (19.0)	632 (1.8)	10 294 (29.6)
Age at diagnosis, years					
<30	384 (1.1)	228 (1.3)	50 (0.8)	7 (1.1)	99 (1.0)
30-39	2652 (7.6)	1462 (8.5)	375 (5.7)	43 (6.8)	772 (7.5)
40-49	6577 (18.9)	3750 (21.7)	904 (13.6)	125 (19.8)	1798 (17.5)
50-59	9729 (27.9)	4390 (25.4)	2061 (31.1)	182 (28.8)	3096 (30.1)
60-69	8335 (23.9)	3988 (23.1)	1751 (26.4)	150 (23.7)	2446 (23.8)
70-79	4605 (13.2)	2244 (13.0)	929 (14.0)	80 (12.7)	1352 (13.1)
≥80	2537 (7.3)	1206 (7.0)	555 (8.4)	45 (7.1)	731 (7.1)
Sex					
Female	34 606 (99.4)	17 102 (99.0)	6600 (99.6)	631 (99.8)	10 273 (99.8)
Male	213 (0.6)	166 (1.0)	25 (0.4)	1 (0.2)	21 (0.2)
Race					
White	250 869 (72.0)	12 780 (74.0)	4799 (72.4)	412 (65.2)	7095 (68.9)
Black	4153 (11.9)	1910 (11.1)	804 (12.1)	94 (14.9)	1345 (13.1)
Asian or Pacific Islander	4994 (14.3)	2295 (13.3)	924 (13.9)	98 (15.5)	1677 (16.3)
American Indian/Alaska Native	362 (1.0)	168 (1.0)	65 (1.0)	20 (3.2)	109 (1.1)
Unknown	224 (0.6)	115 (0.7)	33 (0.5)	8 (1.3)	68 (0.7)
Grade					
I	1604 (4.6)	1196 (6.9)	269 (4.1)	11 (1.7)	128 (1.2)
II	12 271 (35.2)	7310 (42.3)	2471 (37.3)	146 (23.1)	2344 (22.8)
III	18 974 (54.5)	8001 (46.3)	3478 (52.5)	429 (67.9)	7066 (68.6)
IV	99 (0.3)	32 (0.2)	20 (0.3)	1 (0.2)	46 (0.4)
Unknown	1871 (5.4)	729 (4.2)	387 (5.8)	45 (7.1)	710 (6.9)
Histology type (ICD-O-3)[b]					
IDC, 8500	29 553 (84.9)	14 453 (83.7)	5587 (84.3)	548 (86.7)	8965 (87.1)
ILC, 8520	1179 (3.4)	815 (4.7)	246 (3.7)	4 (0.6)	114 (1.1)
Mixed IDC and ILC, 8522	1130 (3.2)	744 (4.3)	212 (3.2)	9 (1.4)	165 (1.6)
Other	2957 (8.5)	1256 (7.3)	580 (8.8)	71 (11.2)	1050 (10.2)
T-staging					
0/is	214 (0.6)	74 (0.4)	44 (0.7)	4 (0.6)	92 (0.9)
mi/1	15 673 (45.0)	8133 (47.1)	3079 (46.5)	219 (34.7)	4242 (41.2)
2	12 391 (35.6)	6321 (36.6)	2264 (34.2)	248 (39.2)	3558 (34.6)
3	2921 (8.4)	1291 (7.5)	575 (8.7)	65 (10.3)	990 (9.6)
4	2460 (7.1)	954 (5.5)	445 (6.7)	63 (10.0)	998 (9.7)
Unknown	1160 (3.3)	495 (2.9)	218 (3.3)	33 (5.2)	414 (4.0)
N-staging					
0/is	20 120 (57.8)	10 300 (59.6)	3868 (58.4)	346 (54.7)	5606 (54.5)
mi/1	14 233 (29.4)	4965 (28.8)	1918 (29.0)	191 (30.2)	3159 (30.7)
2	2196 (6.3)	1060 (6.1)	407 (6.1)	50 (7.9)	679 (6.6)
3	1596 (4.6)	639 (3.7)	296 (4.5)	32 (5.1)	629 (6.1)
Unknown	674 (1.9)	304 (1.8)	136 (2.1)	13 (2.1)	221 (2.1)
M-staging					
0	31 888 (91.6)	16 052 (93.0)	5991 (90.4)	570 (90.2)	9275 (90.1)
1	2827 (8.1)	1165 (6.7)	608 (9.2)	58 (9.2)	996 (9.7)
Unknown	104 (0.3)	51 (0.3)	26 (0.4)	4 (0.6)	23 (0.2)
Bone metastasis					
Yes	1618 (4.6)	786 (4.6)	356 (5.4)	32 (5.1)	444 (4.3)
No	32 714 (94.0)	16 258 (94.2)	6171 (93.1)	591 (93.5)	9694 (94.2)
Unknown	487 (1.4)	224 (1.3)	98 (1.5)	9 (1.4)	156 (1.5)
Brain metastasis					
Yes	247 (0.7)	88 (0.5)	50 (0.8)	7 (1.1)	102 (1.0)
No	34 049 (97.8)	16 932 (98.1)	6472 (97.7)	617 (97.6)	10 028 (97.4)
Unknown	523 (1.5)	248 (1.4)	103 (1.6)	8 (1.3)	164 (1.6)
Liver metastasis					
Yes	1081 (3.1)	367 (2.1)	234 (3.5)	33 (5.2)	447 (4.3)
No	33 245 (95.5)	16 672 (96.5)	6292 (95.0)	592 (93.7)	9689 (94.1)
Unknown	493 (1.4)	229 (1.3)	99 (1.5)	7 (1.1)	158 (1.5)
Lung metastasis					
Yes	885 (2.5)	344 (2.0)	192 (2.9)	19 (3.0)	330 (3.2)
No	33 400 (95.9)	16 667 (96.5)	6329 (95.5)	605 (95.7)	9799 (95.2)
Unknown	534 (1.5)	257 (1.5)	104 (1.6)	8 (1.3)	165 (1.6)
Adjusted AJCC seventh edition stage					
0	78 (0.2)	23 (0.1)	13 (0.2)	3 (0.5)	39 (0.4)
I	12 621 (36.2)	6637 (38.4)	2479 (37.4)	174 (27.5)	3331 (32.4)
II	13 172 (37.8)	6729 (39.0)	2408 (36.3)	255 (40.3)	3780 (36.7)
III	5146 (14.8)	2279 (13.2)	928 (14.0)	115 (18.2)	1824 (17.7)
IV	2829 (8.1)	1165 (6.7)	609 (9.2)	58 (9.2)	997 (9.7)
Unknown	973 (2.8)	435 (2.5)	188 (2.8)	27 (4.3)	323 (3.1)

Continued

Table 1. Continued

Characteristics	All patients	Triple positive	ER+/PR−/HER2+	ER−/PR+/HER2+	ER−/PR−/HER2+
Vital status					
Alive	30 411 (87.3)	15 480 (89.6)	5722 (86.4)	531 (84.0)	8678 (84.3)
Dead attributable to cancer	3044 (8.7)	1126 (6.5)	627 (9.5)	74 (11.7)	1217 (11.8)
Dead attributable to other cause	1364 (3.9)	662 (3.8)	276 (4.2)	27 (4.3)	399 (3.9)

AJCC, American Joint Committee on Cancer; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; is, *in situ*; mi, microinvasion or micrometastasis; PR, progesterone receptor; SEER, Surveillance, Epidemiology, and End Results; triple positive, ER+/PR+/HER2+.
[a] $P < 0.05$ for all comparisons, calculated using the Pearson chi-square test.
[b] By the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) histopathology code.

with the use agreement (ID: 20607-Nov2019). Ethics approval was not required for this study.

Statistical analysis

Demographic and clinical variables of patients with HER2-positive breast cancer were analyzed within subtypes and subgroups using chi-square or Fisher's exact tests as appropriate. The BCSS and overall survival (OS) were defined as the time from diagnosis to death attributed to breast cancer and any cause, respectively. Kaplan—Meier survival curves were used to assess the BCSS. Log-rank tests were used to evaluate differences in survival. Univariable Cox proportional hazards regression analysis was carried out to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of BCSS. Multivariable Cox regression models were used to calculate the HRs and 95% CIs of BCSS and OS after adjusting for age, sex, race, grade, histology type, bone, brain, liver, and lung metastasis, T-, N-, and M-staging, and molecular subtypes. Because the adjusted AJCC seventh edition tumor stage was assessed by tumor size, lymph node status, and distant metastasis, it was removed from the final models to avoid breaching the principle of excluding linearly codependent variables. All statistical analyses were carried out using SPSS 11.3 (International Business Machine, Armonk, NY) and R 3.6.3 software (Lucent Technologies, Murray Hill, NJ). Based on the multivariate model, a nomogram-based model of predictive outcome was set up with RMS and SURVIVAL package from R software. We selected 3-year and 5-year BCSS for analysis in nomogram. One hundred bootstrap resamples were used to produce calibration plots and C-index, which evaluated the predictive accuracy of this nomogram model.

RESULTS

Demographic and clinical features

The study consisted of 34 819 patients, including 34 606 women and 213 men. We outlined the demographic and clinical features of patients with HER2-positive breast cancers based on HR status (Table 1). Triple-positive breast cancer accounted for 49.6% of HER2-positive breast cancer, while ER-positive/PR-negative/HER2-positive, ER-negative/PR-positive/HER2-positive, and ER-negative/PR-negative/HER2-positive subtypes accounted for 19.0%, 1.8%, and 29.6%, respectively. The ER-negative/PR-negative/HER2-positive breast cancer decreased from the percentage of 30.5% to 27.8% in the SEER cohort from 2010 to 2017, while the percentage of the triple-positive breast cancer increased from 48.2% to 51.6%.

As shown in Table 1, patients with ER-positive/PR-negative/HER2-positive breast cancer tended to be older (≥60 years, 48.8%), while patients with triple-positive breast cancer were more frequently aged 49 years or younger. Triple-positive breast cancer was more frequently found in men. The White race was more found in patients with HER2-positive and ER-positive breast cancer. Patients with HER2-positive and ER-positive breast cancer were more frequently of lower tumor grade (grade I-II), lower T-staging (T1), lower N-staging (N0), no brain, liver, and lung metastasis, and lower tumor stage (stage I). However, the percentages of patients with ER-negative and HER2-positive breast cancer were higher in the subgroups of higher tumor grade (grade III-IV), higher T-staging (T2-4), higher N-staging (N1-3), higher M-staging (M1), brain, liver, and lung metastasis, and higher tumor stage (stage II-IV). In addition, the rate of IDC and mixed IDC/ILC in patients with triple-positive or ER-positive/PR-negative/HER2-positive breast cancer was higher than that in patients with ER-negative/PR-positive/HER2-positive and ER-negative/PR-negative/HER2-positive breast cancer.

Prognosis analyses

We next compared the BCSS difference among the four molecular subtypes using unadjusted and univariate analysis. Compared with patients with triple-positive breast cancer, those with ER-positive/PR-negative/HER2-positive (HR = 1.47; 95% CI: 1.33-1.62), ER-negative/PR-positive/HER2-positive (HR = 1.81; 95% CI: 1.43-2.29), and ER-negative/PR-negative/HER2-positive (HR = 1.83; 95% CI: 1.69-1.99) breast cancer had significantly poorer BCSS (all log-rank $P < 0.001$) (Figure 2). Moreover, patients with ER-positive/PR-negative/HER2-positive breast cancer had better BCSS than those with ER-negative/PR-negative/HER2-positive breast cancer (HR = 1.25; 95% CI: 1.14-1.38; log-rank $P < 0.001$). However, no significant differences in BSCC were found between patients with ER-positive/PR-negative/HER2-positive and ER-negative/PR-positive/HER2-positive breast cancer (HR = 1.24; 95% CI: 0.97-1.57) and patients with ER-negative/PR-positive/HER2-positive and ER-negative/PR-negative/HER2-positive breast cancer (HR = 1.01; 95% CI: 0.80-1.28). After adjusting for age, sex, race, grade, histology type, bone, brain, liver, and lung

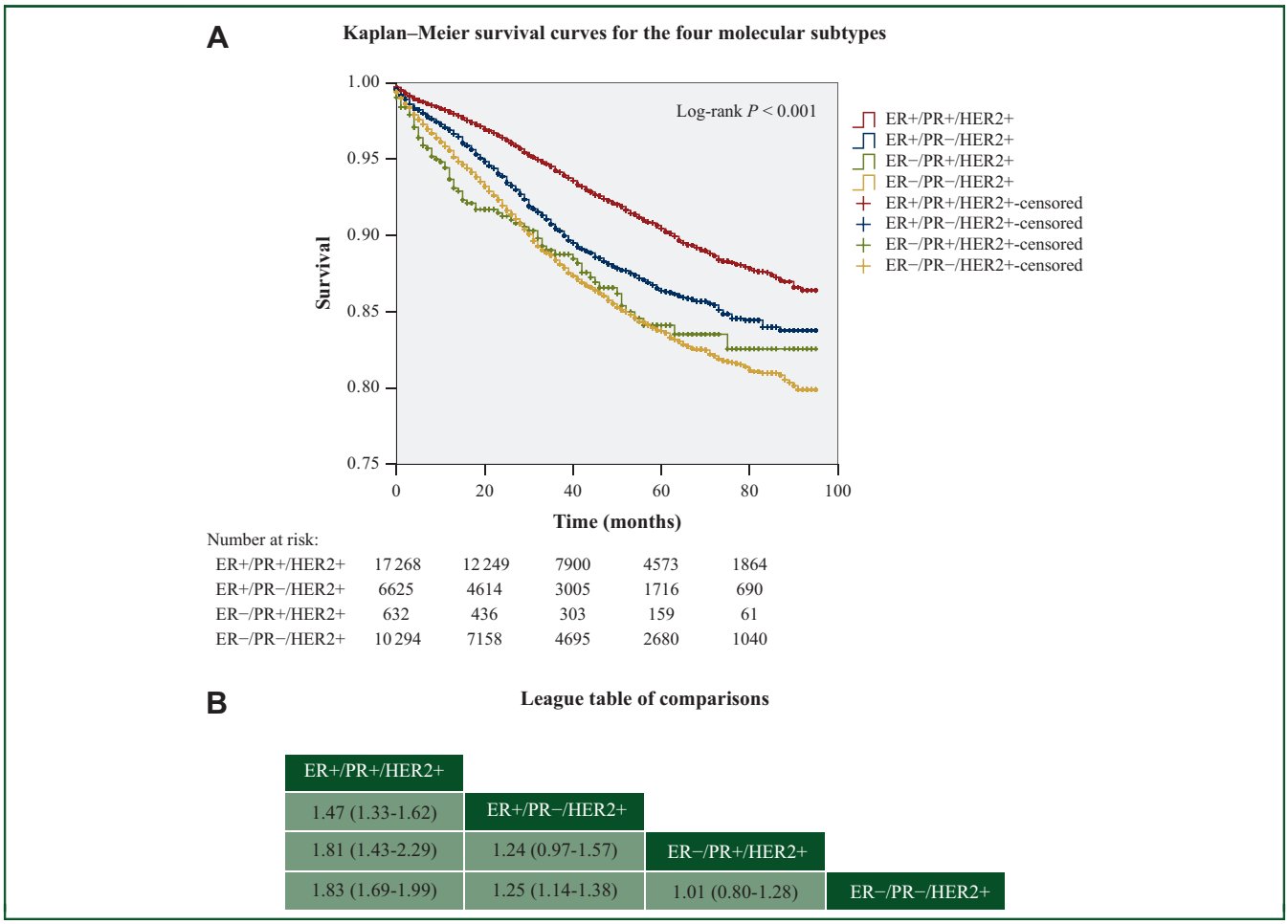

Figure 2. Breast cancer-specific survival of patients with HER2-positive breast cancer stratified by hormone receptor status.
(A) Kaplan—Meier survival curves show breast cancer-specific survival in four molecular subtypes. (B) Data are presented as hazard ratios (95% confidence intervals). A hazard ratio >1 favors the column-defining subtype.
ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.

metastasis, T-, N-, and M-staging, and molecular subtypes in multivariate analyses, patients with ER-positive/PR-negative/HER2-positive (BCSS, HR = 1.26, 95% CI: 1.14-1.39; OS, HR = 1.15, 95% CI: 1.06-1.25), ER-negative/PR-positive/HER2-positive (BCSS, HR = 1.56, 95% CI: 1.23-1.97; OS, HR = 1.43, 95% CI: 1.17-1.75), and ER-negative/PR-negative/HER2-positive (BCSS, HR = 1.56, 95% CI: 1.43-1.70; OS, HR = 1.38, 95% CI: 1.29-1.48) breast cancer still had significantly poorer survival prognosis, compared with those with triple-positive breast cancer, respectively (all log-rank $P < 0.001$) (Table 2). Interestingly, HER2-positive patients in the subgroup of Asian or Pacific Islander had significantly better BCSS (HR = 0.85; 95% CI: 0.76-0.96) and OS (HR = 0.80; 95% CI: 0.73-0.89) than those in the subgroup of other race. However, compared with those with ER-positive/PR-negative/HER2-positive breast cancer, only patients with ER-negative/PR-negative/HER2-positive breast cancer (BCSS, HR = 1.24, 95% CI: 1.13-1.37; OS, HR = 1.20, 95% CI: 1.11-1.30) had significantly poorer survival (log-rank $P < 0.001$) (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2021.100232).

In terms of race (White, Black), tumor grade I-IV, other histology types, and no bone, brain, and liver metastasis, patients with triple-positive breast cancer had significantly better BCSS, compared with those with ER-positive/PR-negative/HER2-positive, ER-negative/PR-positive/HER2-positive, and ER-negative/PR-negative/HER2-positive breast cancer (all log-rank $P < 0.05$), while patients with triple-positive breast cancer had no significant difference in BCSS compared with those with ER-negative/PR-positive/HER2-positive breast cancer in terms of tumor grade I-II and other histology types (Supplementary Table S2 and Figures S2-S7, available at https://doi.org/10.1016/j.esmoop.2021.100232). However, compared with those with ER-negative/PR-positive/HER2-positive breast cancer, patients with ER-negative/PR-negative/HER2-positive breast cancer had significantly better BCSS in terms of age ≥50 years, stage 0-II, bone and brain metastasis, and no lung metastasis (all log-rank $P < 0.05$), while no significant difference was found between patients with triple-positive and ER-positive/PR-negative/HER2-positive breast cancer in terms of bone and brain metastasis, ER-positive/PR-negative/HER2-positive and ER-negative/PR-positive/HER2-positive breast cancer in terms of stage 0-II, and ER-positive/PR-negative/HER2-positive and ER-negative/PR-negative/HER2-positive breast cancer in terms of brain metastasis

Table 2. Multivariable Cox proportional hazards regression analysis for BCSS and OS, based on the SEER database, 2010-2017[a]

Variable	BCSS HR (95% CI)	*P* value	OS HR (95% CI)	*P* value
Age at diagnosis, years				
<30	1 (reference)	NA	1 (reference)	NA
30-39	1.28 (0.84-1.97)	0.25	1.03 (0.70-1.51)	0.89
40-49	1.47 (0.97-2.22)	0.07	1.19 (0.82-1.72)	0.36
50-59	1.71 (1.13-2.56)	0.01	1.53 (1.06-2.21)	0.022
60-69	2.22 (1.48-3.34)	<0.001	2.23 (1.55-3.21)	<0.001
70-79	3.16 (2.10-4.77)	<0.001	4.04 (2.80-5.82)	<0.001
≥80	8.06 (5.34-12.17)	<0.001	11.38 (7.90-16.39)	<0.001
Sex				
Female	1 (reference)	NA	1 (reference)	NA
Male	1.38 (0.94-2.04)	0.10	1.47 (1.09-1.99)	0.013
Race				
White	1 (reference)	NA	1 (reference)	NA
Black	1.49 (1.36-1.64)	<0.001	1.44 (1.33-1.56)	<0.001
Asian or Pacific Islander	0.85 (0.76-0.96)	0.008	0.80 (0.73-0.89)	<0.001
American Indian/Alaska Native	1.48 (1.08-2.02)	0.015	1.56 (1.20-2.03)	<0.001
Unknown	0.21 (0.05-0.84)	0.028	0.21 (0.07-0.64)	0.006
Grade				
I	1 (reference)	NA	1 (reference)	NA
II	1.42 (1.09-1.85)	0.010	1.06 (0.90-1.26)	0.47
III	1.65 (1.27-2.15)	<0.001	1.13 (0.96-1.34)	0.15
IV	2.37 (1.41-4.00)	0.001	1.50 (0.99-2.29)	0.06
Unknown	1.65 (1.24-2.19)	<0.001	1.10 (0.90-1.34)	0.34
Histology type (ICD-O-3)[b]				
IDC, 8500	1 (reference)	NA	1 (reference)	NA
ILC, 8520	1.15 (0.95-1.39)	0.15	1.04 (0.89-1.21)	0.65
Mixed IDC and ILC, 8522	1.07 (0.87-1.31)	0.51	1.04 (0.88-1.23)	0.62
Other	1.01 (0.89-1.13)	0.93	1.02 (0.93-1.13)	0.64
T-staging				
0/is	1 (reference)	NA	1 (reference)	NA
mi/1	0.65 (0.39-1.06)	0.08	0.81 (0.54-1.22)	0.31
2	1.37 (0.84-2.23)	0.21	1.36 (0.91-2.03)	0.14
3	1.72 (1.05-2.82)	0.032	1.70 (1.13-2.56)	0.011
4	2.30 (1.41-3.75)	<0.001	2.20 (1.47-3.31)	<0.001
Unknown	2.11 (1.28-3.48)	0.003	1.98 (1.31-3.00)	0.001
N-staging				
0/is	1 (reference)	NA	1 (reference)	NA
mi/1	1.49 (1.35-1.63)	<0.001	1.23 (1.14-1.32)	<0.001
2	1.88 (1.65-2.14)	<0.001	1.52 (1.37-1.70)	<0.001
3	2.16 (1.89-2.46)	<0.001	1.75 (1.57-1.96)	<0.001
Unknown	2.39 (1.97-2.89)	<0.001	2.08 (1.76-2.44)	<0.001
M-staging				
0	1 (reference)	NA	1 (reference)	NA
1	3.21 (2.82-3.65)	<0.001	2.69 (2.39-3.03)	<0.001
Unknown	0.46 (0.11-1.88)	0.28	0.67 (0.25-1.80)	0.42
Bone metastasis				
Yes	1 (reference)	NA	1 (reference)	NA
No	0.66 (0.58-0.74)	<0.001	0.69 (0.62-0.78)	<0.001
Unknown	1.04 (0.72-1.51)	0.82	1.15 (0.82-1.61)	0.41
Brain metastasis				
Yes	1 (reference)	NA	1 (reference)	NA
No	0.51 (0.43-0.61)	<0.001	0.51 (0.43-0.61)	<0.001
Unknown	0.30 (0.20-0.45)	<0.001	0.27 (0.18-0.40)	<0.001
Liver metastasis				
Yes	1 (reference)	NA	1 (reference)	NA
No	0.60 (0.54-0.68)	<0.001	0.59 (0.52-0.66)	<0.001
Unknown	0.64 (0.44-0.94)	0.022	0.74 (0.52-1.05)	0.09
Lung metastasis				
Yes	1 (reference)	NA	1 (reference)	NA
No	0.74 (0.65-0.83)	<0.001	0.79 (0.70-0.89)	<0.001
Unknown	1.38 (0.99-1.92)	0.06	1.33 (0.97-1.80)	0.07
Molecular subtype				
Triple positive	1 (reference)	NA	1 (reference)	NA
ER+/PR−/HER2+	1.26 (1.14-1.39)	<0.001	1.15 (1.06-1.25)	<0.001

Continued

Table 2. Continued

Variable	BCSS HR (95% CI)	*P* value	OS HR (95% CI)	*P* value
ER−/PR+/HER2+	1.56 (1.23-1.97)	<0.001	1.43 (1.17-1.75)	<0.001
ER−/PR−/HER2+	1.56 (1.43-1.70)	<0.001	1.38 (1.29-1.48)	<0.001

BCSS, breast cancer-specific survival; CI, confidence interval; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hazard radio; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; is, *in situ*; mi, microinvasion or micrometastasis; NA, not applicable; OS, overall survival; PR, progesterone receptor; SEER, surveillance, epidemiology, and end results; triple positive, ER+/PR+/HER2+.

[a] Adjusted for age at diagnosis, sex, race, grade, histology type, bone, brain, liver, and lung metastasis, T-, N-, and M-staging, and molecular subtype.

[b] By the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) histopathology code.

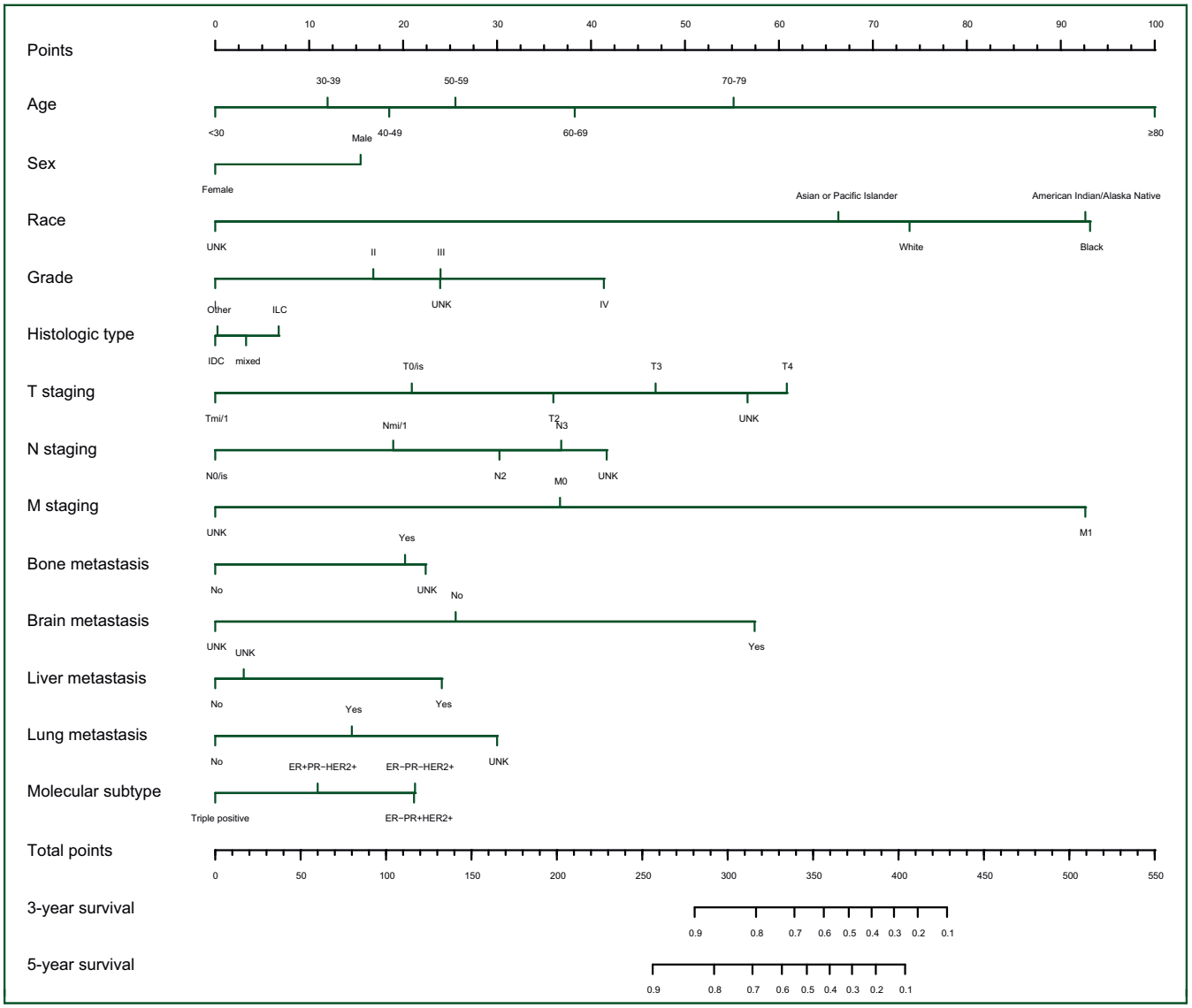

Figure 3. Nomogram for predicting 3-year and 5-year breast cancer-specific survival of patients with HER2-positive breast cancer.
ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; is, *in situ*; mi, microinvasion or micrometastasis; PR, progesterone receptor; triple positive, ER+/PR+/HER2+; UNK, unknown.

(Supplementary Table S2 and Figures S1, S5, S6, S8, and S9, available at https://doi.org/10.1016/j.esmoop.2021.100232). Moreover, there was no significant difference in BCSS between patients with age <50 years, Asian or Pacific Islander, American Indian/Alaska Native, IDC, liver and lung metastasis, and stage III-IV (Supplementary Table S2 and Figures S1, S2, S4, S7, and S9, available at https://doi.org/10.1016/j.esmoop.2021.100232).

Predictive nomogram and validation

A nomogram-based model of predictive outcome was constructed by integrating 13 independent prognostic factors (Figure 3), and the prognosis scores were assigned for each characteristic (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2021.100232). Some variables obtained high scores, such as age ≥80 years (100 points), Black and American Indian/Alaska Native (93/92

points), M1 (93 points), T4 (61 points), and brain metastasis (58 points). The total score for an individual was obtained by adding all scores based on each characteristic. The likelihood of 3-year and 5-year BCSS could be received by drawing a vertical line on the 'total points' axis (Figure 3). The C-index of 0.853 (95% CI 0.845-0.861) suggested a good predictive accuracy for this nomogram-based model. The calibration plots for 3-year and 5-year survival suggested that the predictive survival had been in good line with the recorded prognosis (Supplementary Figure S10, available at https://doi.org/10.1016/j.esmoop.2021.100232).

DISCUSSION

This study analyzed 34 819 patients with HER2-positive breast cancer. The percentages of the four molecular subtypes have changed over the past several years. The rate of triple-positive tumors increased by 3.4% between 2010 and 2017, whereas that of patients with ER-negative/PR-negative/HER2-positive tumors decreased by 2.7%. Several factors may affect hormone levels, such as higher body mass index, early age at menarche, and increased use of hormone therapy.[11] However, between 2010 and 2017, the percentages of patients with triple-positive, ER-positive/PR-negative/HER2-positive, ER-negative/PR-positive/HER2-positive, and ER-negative/PR-negative/HER2-positive tumors remained at approximately 49.5%, 19%, 2%, and 29.5%, respectively, suggesting the existence of the ER-negative/PR-positive/HER2-positive subtype. In previous studies, the percentage of ER-negative/PR-positive breast cancer cases remained at 1%-2% for all breast cancer subtypes,[12-15] which also implies the existence of the ER-negative/PR-positive subtype. In addition, the BCSS was statistically significantly worse in patients with ER-negative/PR-positive tumors than in patients with ER-positive/PR-negative tumors, but better than in patients with the ER-negative/PR-negative subtype.[12,13] ER-negative/PR-positive tumors exhibited an early recurrence and poorer OS compared to ER-positive/PR-positive tumors and had different clinicopathological features compared to other subtypes.[14] In an HER2-negative cohort study, the relapse-free survival (RFS) for ER-negative/PR-positive patients was similar to that for ER-positive patients, but better than that for the triple-negative cases.[16] However, the technical artifacts in immunohistochemistry have been demonstrated as a likely reason for diagnosis of ER-negative/PR-positive cases by repeating the investigation in all cases.[14,15,17] Although there are some technical artifacts in diagnosing ER-negative/PR-positive breast cancer, more and more studies have shown the rare existence of this subtype and its distinct characteristics that are different from other subtypes.

ER-positive/PR-negative breast cancer develops more frequently in older and postmenopausal women.[8,18,19] In this study, ER-positive/PR-negative/HER2-positive tumors were more frequent in patients aged 60 years or older, whereas triple-positive tumors were more frequent in those aged 49 years or younger. Other studies also found that ER-positive/PR-negative/HER2-positive patients tended to be older compared with triple-positive, ER-negative/PR-positive/HER2-positive, and ER-negative/PR-negative/HER2-positive patients.[20,21] Moreover, we showed that White race and male sex were more common in patients with HER2-positive and ER-positive tumors. Previous studies reported that triple-positive and ER-positive/PR-negative/HER2-positive tumors were less likely to be of higher grade (grade III/IV), node positive, and smaller tumor size (T1) than ER-negative/PR-negative/HER2-positive breast tumors.[20,22] In this study, we found a similar pattern in that patients with ER-negative/HER2-positive tumors had more aggressive clinical features, including tumor grade III-IV, T-stage 2-4, N-stage 1-3, M-stage 1, brain, liver, and lung metastasis, and adjusted AJCC seventh edition stage II-IV than those with ER-positive/HER2-positive tumors. Moreover, the triple-positive subtype was associated with a milder tumor behavior than other subtypes. These results suggested that triple-positive tumors represented an independent biological subtype distinct from ER-positive/PR-negative/HER2-positive, ER-negative/PR-positive/HER2-positive, and ER-negative/PR-negative/HER2-positive breast cancer.

Patients with ER-positive/PR-positive breast cancer have better survival than patients with ER-negative/PR-negative tumors.[6,7,23,24] However, data on single HR-positive and triple-positive subtypes are limited. In 2015, Bae et al.[25] reported that there was no difference in survival among the four molecular subtypes in patients with HER2-positive breast cancer. These authors showed that ER-positive/PR-negative and ER-negative/PR-positive subtypes were associated with poor survival similar to the ER-negative/PR-negative subtype in HER2-negative breast cancer. In the present study, we found that patients with ER-positive/PR-negative/HER2-positive, ER-negative/PR-positive/HER2-positive, and ER-negative/PR-negative/HER2-positive subtypes had worse BCSS and OS than patients with the triple-positive subtype. However, there was no significant difference in BCSS between ER-positive/PR-negative/HER2-positive and ER-negative/PR-positive/HER2-positive, or between ER-negative/PR-positive/HER2-positive and ER-negative/PR-negative/HER2-positive subtypes. The present results are consistent with and further strengthen previous evidence.[20,26] After stratifying patients into an HER2-positive group, another study also found significant differences in BCSS between the four molecular subtypes, except when comparing ER-negative/PR-positive subtype with the ER-negative/PR-negative subtype.[12] However, no difference in BCSS was detected in the comparison among these four molecular subtypes in many subgroups in this study. Moreover, compared with the triple-positive subtype, ER loss was statistically significantly associated with an increased risk of breast cancer-specific death (56%) and all-cause death (43%) than PR loss (26% and 15%, respectively). The results of the previous study also indicated that the survival of patients with the triple-positive subtype was superior to that of patients with the ER-positive/PR-negative/HER2-positive subtype, confirming the role of PR in the survival of patients with HER2-positive breast cancer.[27] In

the present study, demographic features (age and race) and clinical variables (T-stage, N-stage, and bone/brain/liver/lung metastasis) were significantly associated with BCSS and OS in HER2-positive breast cancer, and these results were consistent with those of previous studies.[28-30] Among all the distant metastatic sites, brain metastasis was the leading factor related to the survival prognosis, followed by liver, lung, and bone metastasis. A previous study showed similar results regarding the effect of different distant metastasis sites on patient survival.[31] The subgroup of Asian or Pacific Islander had significantly better BCSS and OS than other races, a finding that has not been reported previously.

With regard to therapy, anti-HER2 agents are effective in patients with HER2-positive breast cancer, irrespective of HR expression.[5] However, recent studies showed that heterogeneity existed in patients with HER2-positive breast cancer and is closely related to HR status.[32] Moreover, it is becoming clear that in patients with the HER2-positive subtype, the benefit of anti-HER2 agents may differ according to HR expression. This leads to the speculation of whether HR defines other molecular subtypes in HER2-positive breast cancer.[33] In this study, although it is not possible to define the prognosis of patients with differently expressed HR in triple-positive cases, patients with triple-positive breast cancer may represent an independent biological subgroup that showed a favorable survival among HER2-positive subtypes, and for which the combination of HER2 blockade and endocrine therapy might be considered an excessive medical treatment.[34] However, triple-positive breast cancer shows heterogeneity in its intrinsic subtypes. The luminal A-like triple-positive breast cancer showed a lower HER2 expression and higher HR level than other intrinsic subtypes. This subtype of triple-positive breast cancer might be driven by HR signaling pathways rather than HER2.[34,35] Patients with luminal A-like triple-positive subtype showed significantly better RFS than those with non-luminal A-like triple-positive breast cancer.[20] Thus, we considered the luminal A-like triple-positive breast cancer to represent a special subgroup with a favorable prognosis that might not benefit substantially from anti-HER2 therapy, but could be treated using endocrinotherapy. However, there is a lack of prospective studies to further analyze this strategy and its benefit for luminal-like triple-positive breast cancer.

We developed a nomogram to predict survival outcomes in patients with HER2-positive breast cancer in this study. We included 34 819 patients and identified 13 clinical characteristics as prognostic factors. The C-index assessment and calibration curves suggested that this nomogram-based model of predictive outcome had optimal accuracy. A previous study also developed and validated a nomogram for predicting survival in patients with non-metastatic HER2-positive breast cancer.[36] This is the first large cohort study to construct a nomogram-based model of predictive survival for patients with HER2-positive breast cancer. The nomogram can be feasibly applied in the clinic to predict the survival of each patient with HER2-positive breast cancer, which may help doctors design different treatments according to the expected benefits. Patients who were enrolled in the nomogram analysis represent the major group of HER2-positive patients, which ensures the value of this predictive model for clinical practice.

To the best of our knowledge, this study is the largest analysis focusing on HER2-positive breast cancer carried out to date. The results provided new insight into the epidemiology and clinical characteristics of four different molecular subtypes. Triple-positive breast cancer has distinct survival rates compared with single HR-positive and double HR-negative tumors. Combined with the subtypes of HER2-positive breast cancer, the predictive nomogram developed in this study accurately predicted tumor-specific survival. Further studies and clinical trials are needed to optimize treatment strategies for patients with triple-positive and single HR-positive breast cancer.

The present study had several limitations. The main limitation was the SEER-based retrospective nature of the study. Secondly, data on potential prognostic parameters, such as the Eastern Cooperative Oncology Group performance status score, other tumor metastatic sites, detailed systemic therapy strategies, and the intrinsic subtypes of triple-positive breast cancer, were not included in the SEER database. In addition, only 632 patients with ER-negative/PR-positive/HER2-positive breast cancer were included, and potential bias could not be avoided. Lastly, HER2 status was available after 2010, and the follow-up for most patients was <8 years, which might have disguised the survival difference between molecular subtypes. Further large prospective studies should be carried out and additional potential factors should be considered to improve our predictive model.

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DISCLOSURE

The authors have declared no conflicts of interest.

DATA SHARING

All data used in this paper may be accessed and analyzed via the SEER*Stat web program following the submission of a request for access to the data at https://seer.cancer.gov/seertrack/data/request/.

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